REMARKS

This is in response to the Office Action dated May 15, 2009. In the Office Action, claims1-5 and 14-37 are pending and stand rejected.

The Office Action rejected claims 1-5 and 14-37 under 35 USC 112, first paragraph. The Office Action asserted that the Specification while enabling for a Rhytisma fulvum fraction with neuroactivity in a cockroach does not reasonably provide enablement for neuroactivity in general by a compound of formula (0) or more specifically by the compound of formula (II). The Office Action indicated that the Specification does not enable a person of skill in the art to make and use the invention commensurate in scope with these claims. The Office Action alleged that while the isolation of a Rhytisma fulvum fraction with neuroactivity in a cockroach is described in the instant Specification, there is no information relating to the assignment of the formula (0) or of the formula (II) and that this information can not be deduced from chromatographic Rf and retention time values. The Office Action also indicated that the instant Specification offers no direction regarding the chemical synthesis of a compound of formula (0) or formula (II) and that natural products due to their conformational dependence are well known for being extremely difficult to chemically synthesize and would not be synthetically obvious to one of skill in the art. The Office Action cited a number of undue experimentation factors, i.e. quantity of experimentation, amount of guidance, etc. for making an enablement rejection. The Office Action concluded that characterization of the active component of Rhytisma fulvum fraction, synthesis of the compound of formula (0) and formula (II) is not disclosed, would require extensive experimentation with a highly skilled artisan and is an unpredictable art.

In response to the Office Action, Applicants present evidentiary data to support the claimed invention in the form of a Declaration. See attached Declaration. The Declaration is presently being signed by one of the inventors and a signed copy will be provided very soon.

The data in the Declaration can be obtained by a person or persons of ordinary skill in the art. Applicants assert that in the field of synthetic and analytic chemistry that a person of ordinary skill generally has a Ph.D and is highly skilled. Thus, the characterization that a highly skilled artisan is needed should not be a factor in the rejection because in this art, a person of

ordinary skill is a highly skilled person. Furthermore, Applicants assert that all of the chemical reactions implemented in the synthetic pathways shown in the Declaration are well known in the art to a person of ordinary skill and also other well-known chemical reactions could be implemented in order to obtain the same intermediates and final compound.

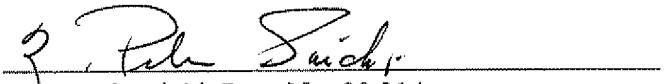
Applicant assert that the amount of direction or guidance presented and the experimentation necessary are well within the skill of a person of ordinary skill in the art. The person of skill in the art can use the knowledge known in the art and the disclosure in the Specification to practice the invention without undue experimentation and with a reasonable expectation of success. While the chemical arts may be at times unpredictable, Applicants assert that the knowledge in the art regarding the elucidation of structure, characterization of neuroactivity and synthesis of the compounds when combined with the teachings in the Specification provide sufficient guidance to predictably practice the claimed invention. Given the discussion above, Applicants assert that the breadth of the claims is commensurate with the teachings of the Specification.

Based on above discussion and the attached Declaration, Applicants assert that the claims, as written are allowable and respectfully request the allowance of the claims.

The Director is authorized to charge any fee deficiency required by this paper or credit any overpayment to Deposit Account No. 23-1123.

Respectfully submitted,

WESTMAN, CHAMPLIN & KELLY, P.A.

By: 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Katrina-Ethel Petit et al.	Confirmation No.: 1347
Appln. No.	:	10/581,226	Group Art Unit: 1625
Filed	:	June 2, 2006	Examiner: David E. Gallis
For	:	NEUROACTIVE SUBSTANCE AND USES OF ONE SUCH SUBSTANCE	
Docket No.	:	U25.12-0001	

DECLARATION UNDER 37 C.F.R. § 1.132

VIA ELECTRONIC FILING

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Karina-Ethel Petit hereby declare as follows:

1. I am a co-inventor of the subject matter of the above-identified patent application.

2. I am currently ___[**Please provide title of your current position**] at Universite De Nantes, in Nantes, France.

3. My Curriculum Vitae is attached hereto as Exhibit A. [**Please provide if available.**]

4. I declare that with respect to the structure and conformation of the compounds, the molecular formula $C_{16}H_{24}O_5$ for fulvol acetate isolated from the soft coral Rhytisma fulvum was established by HRESIMS ($[M+Na]^+$ m/z 319.1521, calcd 319.1524, Δ -0.3 mmu) and it indicated 5 degrees of insaturation. Fulvol compound was also isolated from the soft coral Rhytisma fulvum and was used for stereochemistry elucidation of fulvol acetate. The molecular formula $C_{14}H_{22}O_4$ for fulvol isolated from the soft coral Rhytisma fulvum was established by HRFABMS ($[M+H]^+$ m/z 255.1594, calcd 255.1596, Δ -0.2 mmu) and it indicated 5 degrees of insaturation. The relative structures of fulvol and fulvol acetate were solved by their DEPT ^{13}C spectra and by

two-dimensional NMR studies (See attached Table 1).

5. I also declare that excellent quality crystals of fulvol were spontaneously obtained. X-ray crystallographic analysis elucidated the relative configuration and fulvol was finally deduced to be 6α-acetyl-4β, 5β-dimethyl-1(10)α-epoxy-2α, 7α-dihydroxy-decalin. Total acetylation of fulvol and fulvol acetate led to the same fully acetylated product (complete matching of the NMR spectra) indicating that fully acetylated derivatives of fulvol and fulvol acetate had the same stereochemistry, it was concluded that accordingly fulvol and fulvol acetate have also the same stereochemistry. This was confirmed by similar [α]20D values in CH_3OH and similar NMR data.

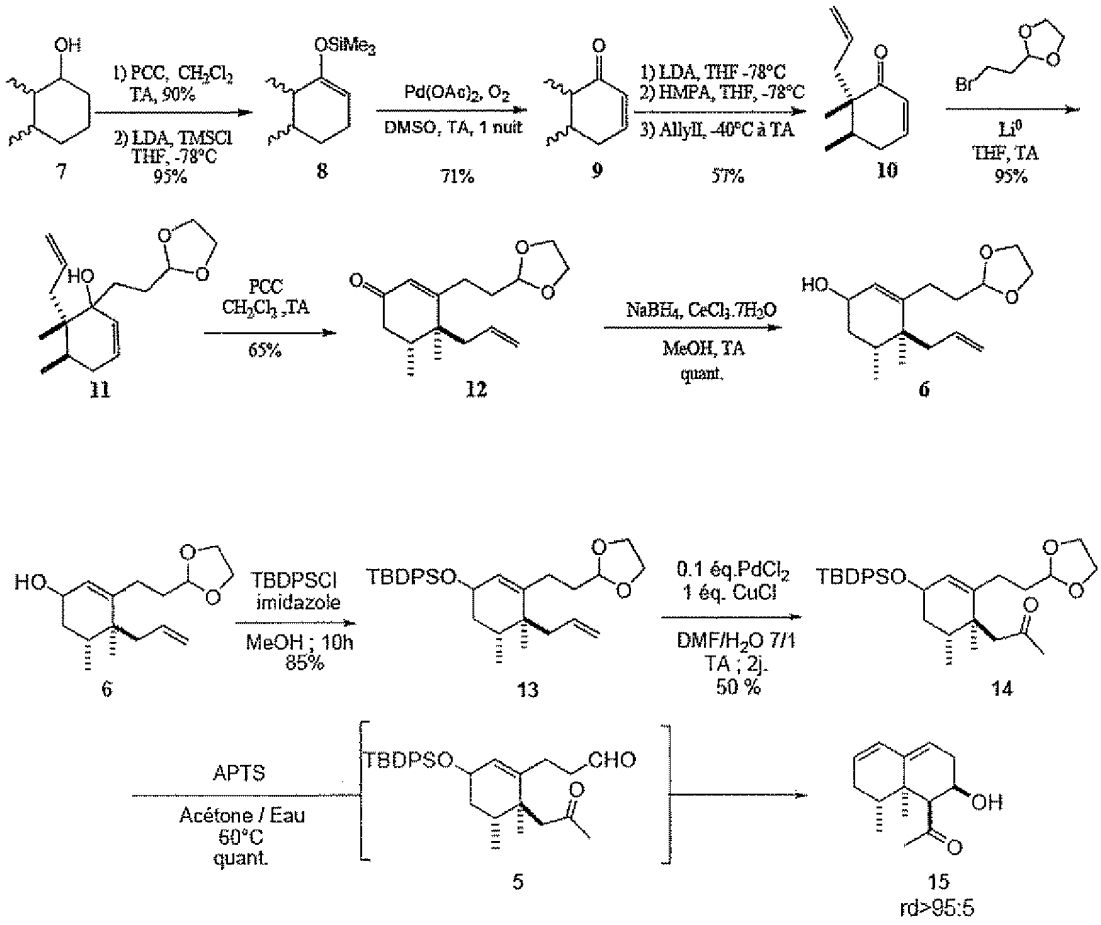
6. I further declare that based on these results, it is reasonable to assume that the fulvol acetate isolated from the soft coral Rhytisma fulvum corresponds to 6α-acetyl-4β, 5β-dimethyl-1(10)α-epoxy-2α-hydroxy-7α-acetoxydecalin (compound of formula II).

7. I declare that with respect to the neuroactivity of the compounds, the effect of fulvol acetate (compound of formula II) was examined on insect neurosecretory cells named DUM neurons. These DUM neurons are known to display beating spontaneous electrical activity (Grolleau and Lapied 2000; Wicker et al. 2001). DUM neurons were pretreated with 4-AP, a specific blocker of the A-type potassium current known to regulate the firing frequency (Grolleau and Lapied 2000). Under these conditions, the somata of DUM neurons generated a spontaneous firing (about 1-3 Hz in frequency) of action potential (Fig. 1B) Bath application of 100 μM of fulvol acetate produced an important increase in the action potential discharge frequency without any modification of the firing pattern and action potential amplitude but reducing the spike interval and increased the slope of the predepolarization.(Fig. 1C and 1E). This effect was associated with a slight increase of the amplitude of the posthyperpolarization (Fig. 1D).

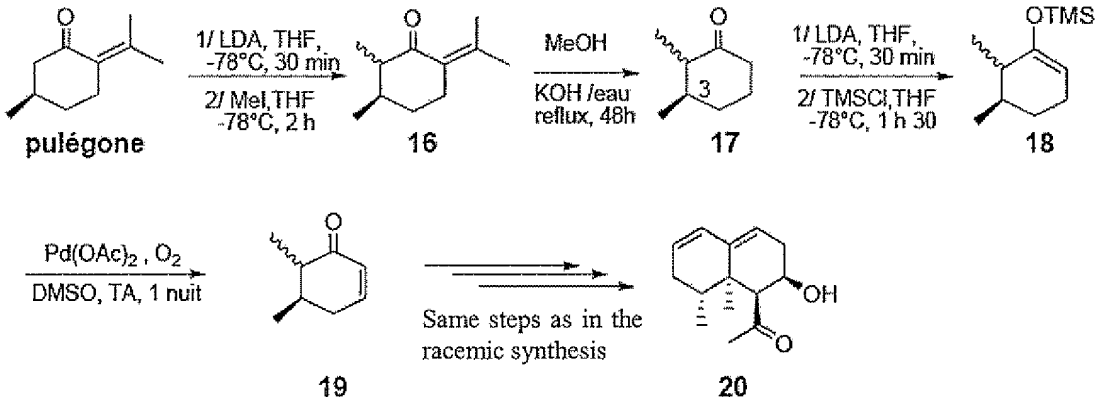
8. I further declare that additional experiments were performed, under voltage-clamp condition, in order to study the effect of fulvol acetate on the global LVA calcium currents, the maintained component mLVA calcium current and the HVA calcium current. As illustrated in Fig. 2Aa, 2Ac and 2Ba, fulvol acetate only strongly increased the peak total LVA calcium current amplitude without any effect on both mLVA current and HVA calcium current (Fig. 2C and 2F). Fulvol acetate-induced stimulation of current amplitude reached a maximum stable level within about 8 minutes (Fig. 2D).

9. I also declare that in addition, experiments were also performed on native whole-cell T-type currents recorded in brain slices in the region of the thalamus containing mRNA for the three fid-fferent isoforms: reticular thalamic nucleus (nRT) (Cav3.2 and Cav3.3), ventro-basal (VB) nucleus (Cav3.1) as well as dorsal root ganglion (DRG) cells containing largely Cav3.2 (Talley et al. 1999). As illustrated in Figures 3C and 3D, external applications of fulvol acetate increased the amplitude of native rat neuronal T-type current elicited by a test-potential to -50 mV (nRT and VB neurons) or -30 mV (DRG neurons) from holding potential of -100 mV.

10. I declare that with respect to the chemical synthesis of the compounds, the synthetic pathways are depicted below. For racemic synthesis, the different steps of the synthetic pathway leading from the dimethyl-cylohexanol compound 7 to the intermediate 15 (1-(2-hydroxy-8,8a-dimethyl-2,3,7,8,8a,1-hexahydro-naphthalenyl)-ethanone) in the fulvol acetate (compound of formula II) synthetic pathway, are depicted below:

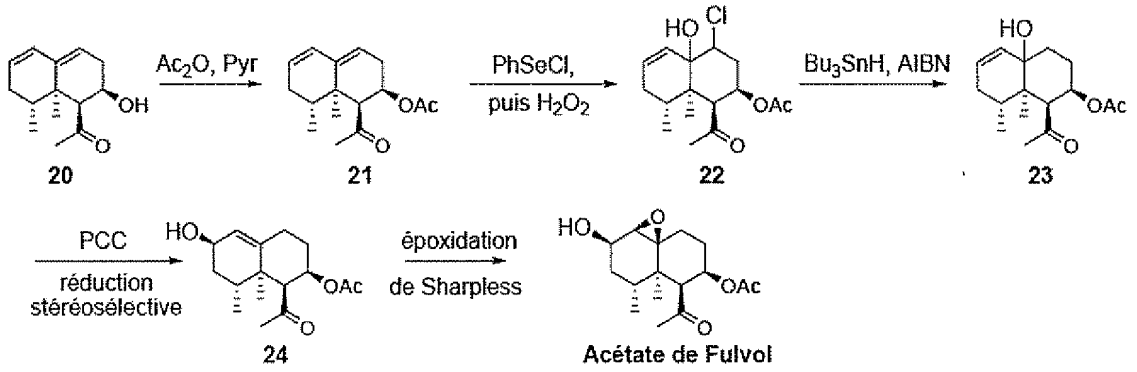


11. I declare that with respect to pure-enantiomeric synthesis, the different steps of an alternative synthetic pathway leading from the pulegone compound to a precursor 20 of fulvol acetate (compound of formula II) are depicted below:



Dimethyl-cyclohexanol compound

12. I declare that with respect to synthesis for intermediate 15 or 20 to fulvol acetate (compound of formula II), the final steps of the synthetic pathway leading to fulvol acetate compound are as follows:



13. I declare that all the chemical reactions implemented in theses synthetic pathways are well-known to a person of ordinary skill in the art and that other well-known chemical reactions could be implemented in order to obtain the same intermediates and final compound.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Inventor: Karina-Ethel Petit
(Printed Name)

Inventor: _____
(Signature)

Date: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	Katrina-Ethel Petit et al.	Confirmation No.: 1347
Appln. No.	:	10/581,226	Group Art Unit: 1625
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EXHIBIT A

OF

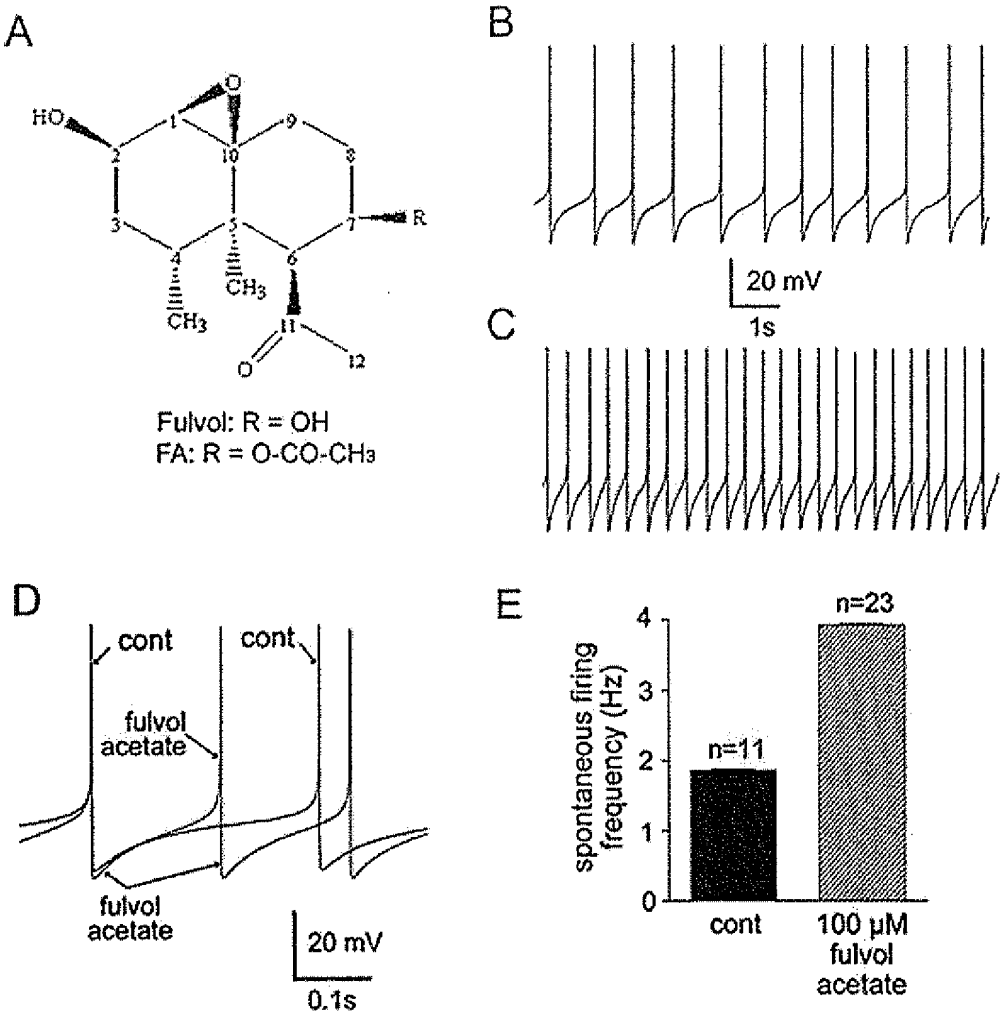
DECLARATION UNDER 37 C.F.R. § 1.132

[Attach Curriculum Vitae of inventor]

Table 1. *^{1}H NMR and ^{13}C NMR Data for Fulvol and Fulvol Acetate in CD_3OD, 500 MHz*

	Fulvol		Fulvol Acetate	
Position	δC	δH (*J* in Hz)	δC	δH (*J* in Hz)
1	61.2	3.0, dd (0.96, 3.4)	61.1	3.05, dd (1.0, 3.5)
2	64.8	4.0, ddd (1.4, 3.3, 8.0)	64.6	4.05, ddd (1.4, 3.4, 7.9)
3	36.6	1.3, brd (1.3, 4.8, 15.4)	36.5	1.38, ddt (1.3, 4.7, 15.4)
		1.6, ddd (8.1, 12.4, 15.4)		1.66, ddd (8.0, 12.4, 15.4)
4	29.5	2.0, ddd (5.0, 6.8, 12.1)	29.5	2.02, m (1.8, 6.7)
5	40.6		41.2	
6	61.5	3.3, d (6.02)	58.3	3.39, d (6.0)
7	69.2	4.2, ddd (4.9, 6.0, 12.0)	72.5	5.40, ddd (5.1, 6.5, 12.2)
8	28.3	1.75, m (1.3, 4.8, 15.4)	25.3	1.86, m (1.0, 2.4, 12.4)
		2.1, ddt (4.5, 12.4, 14.0)		2.28, ddt (4.6, 12.4, 14.0)
9	30.1	1.2, ddd (2.5, 4.4, 14.4)	29.7	1.29, ddd (2.5, 4.5, 14.3)
		2.3, dt (4.6, 14.3)		2.41, dt (4.7, 14.2)
10	65.4		65.0	
11	212.7		211.0	
12	35.1	2.3, dt (4.6, 14.3)	34.2	2.33, s
13	16.0	0.8, d (6.8)	15.9	0.81, d (6.8)
14	17.7	1.0, s	17.5	1.09, s
15			171.8	
16			21.0	2.04, s

Figure 1



Fulvol: R = OH
FA: R = O-CO-CH3

Figure 2

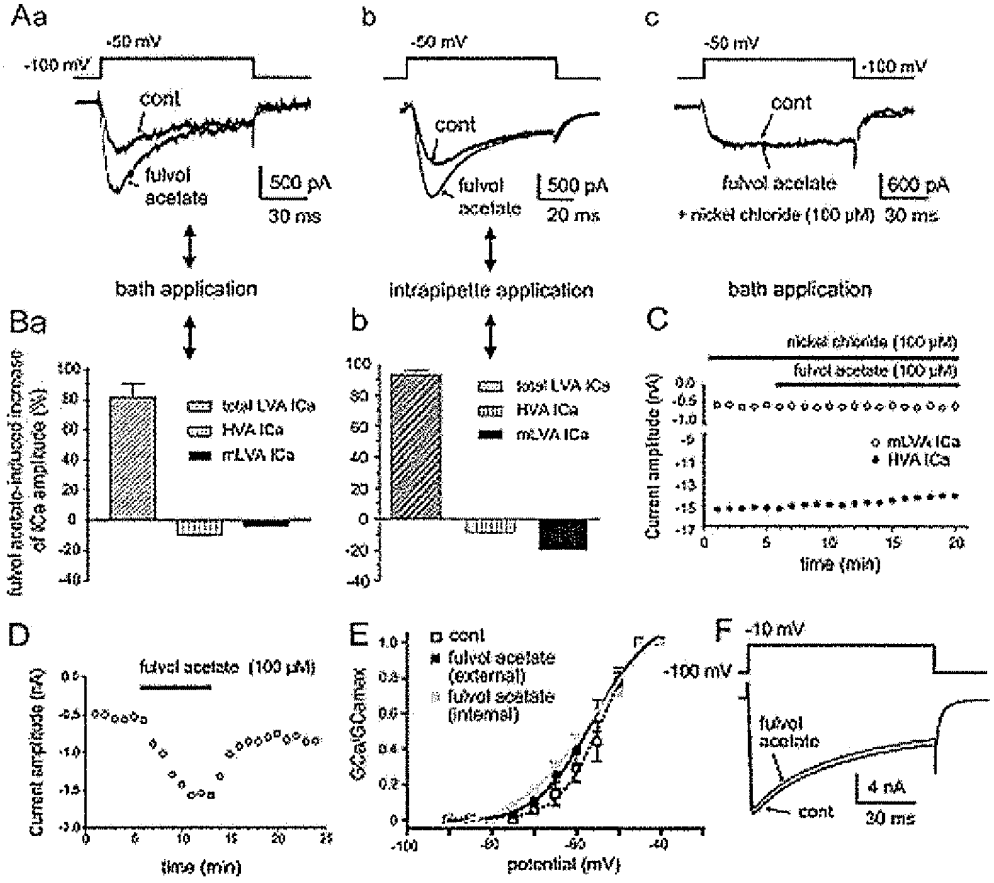
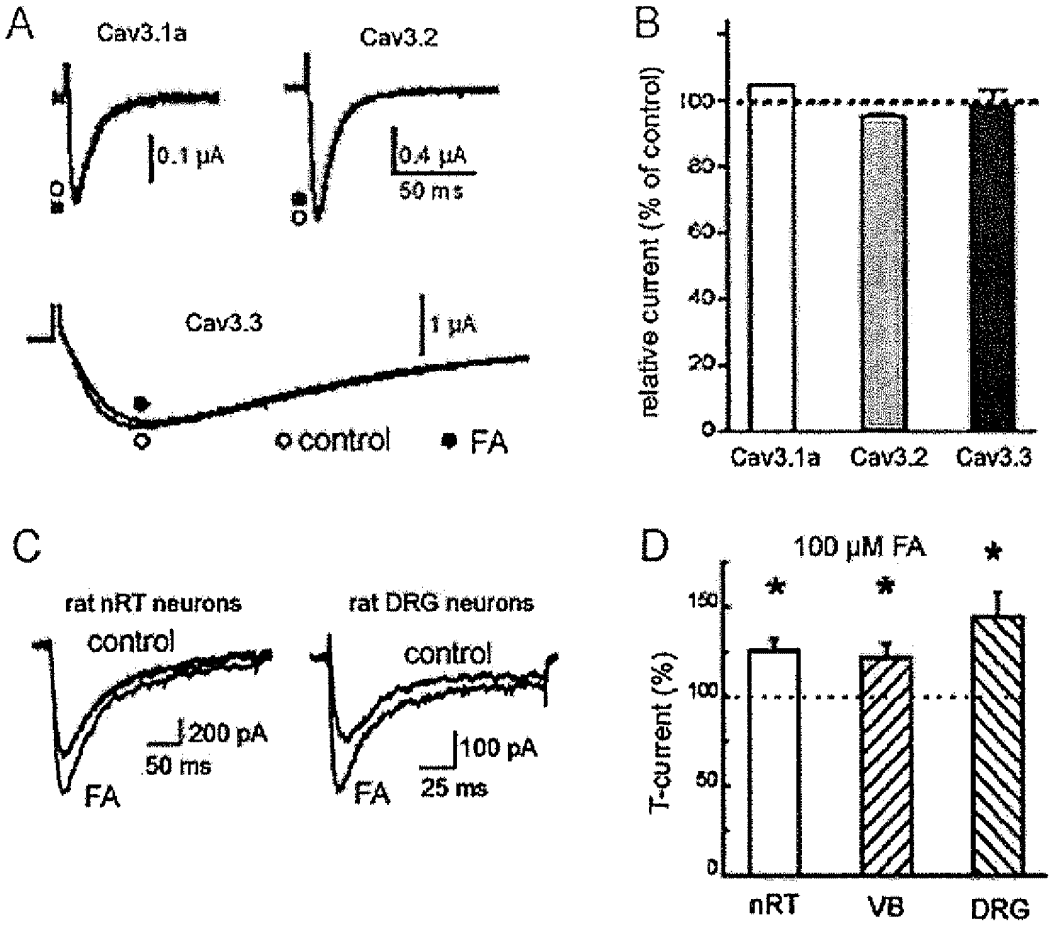

Aa
-50 mV
-100 mV
cont
fulvol acetate
500 pA
30 ms
bath application
b
-50 mV
cont
fulvol acetate
500 pA
20 ms
intrapipette application
c
-50 mV
-100 mV
cont
fulvol acetate
600 pA
+ nickel chloride (100 µM) 30 ms
bath application
Ba
fulvol acetate-induced increase of ICa amplitude (%)
total LVA ICa
HVA ICa
mLVA ICa
b
total LVA ICa
HVA ICa
mLVA ICa
C
nickel chloride (100 µM)
fulvol acetate (100 µM)
Current amplitude (nA)
mLVA ICa
HVA ICa
time (min)
D
fulvol acetate (100 µM)
Current amplitude (nA)
time (min)
E
cont
fulvol acetate (external)
fulvol acetate (internal)
ICa/ICamax
potential (mV)
F
-10 mV
-100 mV
fulvol acetate
cont
4 nA
30 ms

Figure 3


A
Cav3.1a
0.1 µA
Cav3.2
0.4 µA
50 ms
Cav3.3
1 µA
control
FA
B
relative current (% of control)
100
80
60
40
20
0
Cav3.1a
Cav3.2
Cav3.3
C
rat nRT neurons
control
200 pA
50 ms
FA
rat DRG neurons
control
100 pA
25 ms
FA
D
100 µM FA
*
*
*
T-current (%)
150
100
50
0
nRT
VB
DRG